UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/170,980	10/13/1998	JENNIFER L. HILLMAN	PF-0195-2 RCE	7498

27904 7590 04/10/2003

INCYTE CORPORATION (formerly known as Incyte Genomics, Inc.)
3160 PORTER DRIVE
PALO ALTO, CA 94304

EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/10/2003

34

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/170,980	Applicant(s) HILLMAN ET AL.	
	Examiner MINH-TAM DAVIS	Art Unit 1642	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,18-20 and 26-32* is/are pending in the application.

4a) Of the above claim(s) *27-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,18-20 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/21/03 has been entered.

Applicant cancels claim 25 in paper No: 27.5 of 12/18/02.

Accordingly, claims 1, 18-20, 26 are being examined.

The following are the remaining rejections.

OBJECTION

Claim 26 is objected to because it is drawn to the same composition as claim 20, i.e, is a composition comprising a polypeptide of claim 1 and a suitable pharmaceutical carrier.

Applicant is advised that should claim 20 be found allowable, claim 26 will be rejected under 35 U.S.C. 101 as being a substantial duplicate thereof, When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to

reject the other as being a substantial duplicate of the allowed claim. See MPEP 706.03(k).

REJECTION UNDER 35 USC 101, UTILITY

Rejection under 35 USC 101 of claims 1, 18-20, 26 pertaining to lack of a specific and/or substantial utility remains for reasons already of record in paper No.21.

1. Answers to arguments in paper No:25, on 11/16/02.

Applicant argues in paper No:25 as follows:

Applicant argues that the claims have patentable utility and a well known utility based on 1) the strong chemical and structural homology of the claimed HPAK protein (SEQ ID NO:1) with a known human pancreatic kallikrein (54% sequence identity), and 2) the presence of three conserved, non-contiguous amino acid residues H65, D113 and S206, for serine protease, which is likely to confer chymotrypsinogen-like activity to HPAK, 10 conserved cysteines, which are structurally important and involved in the formation of 5 disulfide bonds, as well as one conserved amino acid D200, which is likely to confer chymotrypsinogen-like activity to HPAK, and at the amino terminal end, 24 amino acids which are similar to signal sequences important for kallikrein secretion. Applicant asserts that thus the claimed HPAK protein has numerous practical, beneficial uses in toxicology testing, drug development and the diagnosis of diseases characterized by expression of HPAK, none of which necessarily require detailed knowledge of how the polypeptide coded for by the polynucleotide works.

Applicant asserts that there is more than enough homology to demonstrate a reasonable probability that the utility of human pancreatic kallikrein can be imputed to the claimed invention, since Brenner et al teach that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small.

Applicant submits a signed Declaration by Lars Michael Furness, describing how the claimed polypeptide can be used in protein expression analysis such as 2-D PAGE gels and Western blot.

Applicant's arguments set forth in paper No.25 have been considered but are not deemed to be persuasive for the following reasons:

The recitation of the reference by Brenner et al, and the submission of the signed Declaration by L.M. Furness is acknowledged.

Concerning Applicant's assertion that the claims have patentable utility and a well known utility based on the strong chemical and structural homology of the claimed HPAK protein (SEQ ID NO:1) with known human pancreatic kallikrein, and the presence of three conserved, non contiguous amino acid residues H65, D113 and S206, for serine protease, and 10 conserved cysteines, as well as one conserved amino acid D200, this argument is not persuasive because based on sequence identity alone, one could not predict the function of a protein, as taught by Bowie et al, Lazar et al and Burgess et al, all of record (See further discussion of this issue and the Declaration by L.M. Furness below).

I. <u>The Applicable Legal Standard</u>

Applicant refers to the recitation of the case law on the utility requirement at pages 7-8 in the response of paper No:17 on 04/26/02.

II. Toxicology testing, drug discovery and disease diagnosis

A. Similarity with kallikrein 11

Applicant asserts that it is more likely than not that, similar to human kallikrein 11, which has serine protease activity, the claimed SEQ ID NO:1 would also have serine protease activity, because of the following reasons: i) SEQ ID NO:1 has 90% overall sequence identity with kallikrein 11 (also known as hippostasin, PRSS20, KLK11, and TLSP, g18314498, Exhibit B), wherein both the trypsin-like serine protease and trypsin domains within human kallikrein 11 are also present within SEQ ID NO:1 (Exhibit A, L61-N253, and R24-I254 of Exhibit C), ii) The presence of amino acids H65, D113 , S206 and D200 in SEQ ID NO:1, wherein said amino acids are known to be essential for serine protease activity, as described by Yousef, GM et al, page 91-92, in Exhibit F, iii) There is structural homology of SEQ ID NO:1 with g9296987 within the disulfide bonds region, a protein belonging to the peptidase family S1 and the Kallikrein subfamily (Exhibit E), and iv) expression profile of SEQ ID NO:1 as presented in figure 5. Applicant further asserts that secretion is a property of a serine protease, as disclosed by Olsson et al in Exhibit I.

Applicant asserts that the teaching of Bowie et al, Lazar et all, Burgess et al, and Bork are not applicable for the above reasons, and for reasons recited in previous response of paper NO:17.

Concerning whether the deduced amino acid sequence of SEQ ID NO:1 is expressed or associated with various cancer, Applicant asserts that since kallikrein 11 is found in brain, skin and prostate, as shown by Yousef,GM et al, 2000, in Exhibit F, Mitsui, S et al, 2000, in Exhibit G, and Nakamura, T et al, 2001, in Exhibit H, it is more likely than not that SEQ ID NO:1 is also expressed, predominantly in prostate tissue.

The recitation of Olsson et al, Yousef,GM et al, Mitsui, S et al, and Nakamura, T et al is acknowledged.

Applicant's arguments set forth in paper No.25 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that there is no expression profile of the polypeptide of SEQ ID NO:1 in figure 5 of the specification, which shows the results of electronic Northern analysis of SEQ ID NO:2, which is claimed to encode SEQ ID NO:1 (p.3, figure 5 legend).

SEQ ID NO:1 has not been shown to be functionally related to a human pancreatic kallikrein nor kallikrein 11. Applicant has not shown which amino acid residues constitute the trypsin-like serine protease and trypsin domains within human kallikrein 11, and that these domains are also present within SEQ ID NO:1. The only showing is that the protein of SEQ ID NO:1 presumably encoded by the claimed polynucleotide of SEQ ID NO:2 has 54% or 90% sequence identity to a human pancreatic kallikrein, or kallikrein 11, respectively . Although the human pancreatic kallikrein and kallikrein 11 have protease activy, neither the specification, nor the art of record teaches any association of SEQ ID NO:1 with a protease or chymotrypsinogen activity. Moreover, although SEQ ID NO: 1 has three non-contiguous conserved amino acids of serine

proteases, and one conserved amino acid D200, there is no indication that these three non-contiguous conserved amino acids and said amino acid D200 would confer serine protease activity to SEQ ID NO:1. Similarly, although SEQ ID NO:1 has 10 conserved cysteines, which are involved in the formation of 5 disulfide bonds, there is no indication that these cysteines would form disulfide bonds in SEQ ID NO:1. Even if these cysteines form disulfide bonds in SEQ ID NO:1, and although formation of disulfide bonds would confer some structural conformation to SEQ ID NO:1, there is no indication that said conformation would confer serine protease activity to SEQ ID NO:1. Further, there is no teaching of consensus sequences that would suggest that the claimed SEQ ID NO:1 is part of the same human pancreatic kallikrein. Moreover, with a 54% or 90% sequence identity with a human pancreatic kallikrein, or kallikrein 11, respectively, one could not predict that the claimed SEQ ID NO:1 has the same function as a human pancreatic kallikrein, or kallikrein 11, based on the teaching of Bowie et al, Lazar et al, Burgess et al, and Bork. Because the differences between SEQ ID NO:1, a human pancreas kallikrein and kallikrein 11 involves 46% and 10%, amino acid differences, respectively, as previously disclosed, the effects of these differences upon protein function cannot be predicted since as taught by Bowie et al, the amino acid sequence determines the shape and function of a protein and it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. The Lazar et al and Burgess et al references, although drawn to site directed mutagenesis studies, clearly demonstrate that even a single amino acid alteration can alter the function of a protein. It would be expected that with

the disclosed differences in amino acid composition, at least some of the amino acids required for any common function would be altered. Although the proteins show some identity, such as three non-contiguous amino acids, and 10 cysteines, and one amino acid D200, no conserved region with any protease function has been identified. As previously disclosed, with these percent dissimilarities between the polypeptide encoded by the claimed invention and the prior art proteins, the effects of these dissimilarities upon protein structure and function cannot be predicted. Further, although it is clear that methods are available to identify proteins with identity between primary amino acid sequences, it is well known and clearly understood in the art, as taught by Bowie et al that prediction of protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex, and it is also well known in the art, as exemplified by Lazar et al and Burgess et al that even a single amino acid change can alter protein function. The unpredictability of utilizing predicted structural determinations to ascertain functional aspects of the protein is further demonstrated by Bork, of record, who teaches the pitfalls associated with comparative sequence analysis for predicting protein function. Bork specifically states that conclusions from comparison analysis are often stretched with regard to protein products and specifically cites that most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality.

Concerning the expression of SEQ ID NO:1 in nature in cancer prostate tissue, and /or overexpressed in cancer tissues as compared to normal tissues, the expression of

kallikrein 11 protein in brain, skin and prostate cannot be used to predict the expression of SEQ ID NO:1, because expression of different sequences are different and independent of each other, and because SEQ ID NO:1 is not kallikrein 11. As discussed in previous Office action, it is unpredictable that SEQ ID NO:1, which is a deduced amino sequence from the polynucleotide of SEQ ID NO:2, is expressed in cancer tissue in nature and /or overexpressed in cancer tissues as compared to normal tissues. The references by Alberts et al, Shantz et al, and Fu et al (all of record) clearly indicate that the presence of mRNA does not always dictate that such mRNAs are translated into proteins, and that the predictability of protein translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. For example, the p53 protein levels of expression do not correlate with levels of p53 mRNAs, and the p53 protein could be undetectable in cells expressing abundant amount of wild type p53 mRNA (Fu et al, of record, figure 3, and page 4396, second column). Further, the intracellular half-life of ornithine decarboxylase is less than 1 hour, and the post-translational regulation of the degradation of said enzyme is depending on the level of polyamines (Shantz et al, of record, page 110, first column).

B. The use of HPAK (SEQ ID NO:1) for toxicology testing, drug discovery and disease diagnosis.

Applicant argues that the claimed polypeptide is useful as tools for toxicology testing, drug discovery, and the diagnosis of diseases that confer "specific benefits" to the public. Specifically, Applicant refers to a Declaration by Lars Michael Furness, stating that the claimed invention is useful in two-dimensional gel electrophoresis

analysis and Western blot used to monitor protein expression and assess drug toxicology. Applicant argues that as shown in Exhibit A, results of BLASTP analysis, not only SEQ ID NO:1 is expressed, but it has been identified by numerous separate groups. Applicant recites the references by Gan L et al, 2000, Exhibit J, abstract only, and Yousef, GM et al , 2001, Exhibit K, as supporting references. Applicant concludes that therefore, SEQ ID NO:1 is useful in two-dimensional gel electrophoresis analysis and Western blot used to monitor protein expression and assess drug toxicology.

The recitation of the references by Gan et al and Yousef et al is acknowledged.

Applicant's arguments set forth in paper No.25 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that the references by Gan et al and Yousef et al only recite kallikrein family and not the claimed SEQ ID NO:1.

It is also noted that toxicology testing and drug discover are not specifically recited in the specification as originally filed. Similarly, the use of two-dimensional gel electrophoresis analysis and Western blot to monitor the expression of SEQ ID NO:1, and assess drug toxicology is not specifically recited in the specification as originally filed.

It is further noted that SEQ ID NO:1 is a deduced amino acid sequence from a polynucleotide sequence of SEQ ID NO:2. The specification only discloses detection of mRNA of SEQ ID NO:2 in various cancer tissues. It is unpredictable that SEQ ID NO:2 would express and/or overexpress as proteins in cancer tissues, or in tissues involved in immune response, because it is well known in the art that a gene could be regulated

at different levels, transcriptional, translational and postranslational regulation and that not all mRNA express as proteins (Alberts et al, Shantz et al, and Fu et al, all of record; *supra*).

Further, concerning the argument that that the claimed invention is useful in two-dimensional gel electrophoresis analysis and Western blot used to monitor protein expression and assess drug toxicology, the argument is not persuasive, because for a utility to be "well-established" it must be specific, substantial and credible. In this case, as indicated by Applicant, all nucleic acids and expressed genes are in some combination useful in toxicology testing. However, the particulars of toxicology testing with the claimed SEQ ID NO: 1 are not disclosed in the instant specification. Neither the toxic substances nor the susceptible organ systems are identified from drug screening using two-dimensional gel electrophoresis. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to SEQ ID NO:1. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed polypeptide in an array for toxicology screening or expression profiling is only useful in the sense that the information that is gained from the array or profile is dependent on the pattern derived from the array or profile, and says nothing with regard to each individual member of the array or profile. Again, this is a utility which would apply to virtually every member of a general class of

materials, such as any collection of proteins or DNA. Even if the expression of Applicant's polypeptide is affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the claimed polypeptide has no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding the polypeptide could be put.

Further, in the absence of any disclosed relationship between the claimed polypeptide and any disease or disorder and the lack of any correlation between the claimed polypeptide with any known disease or disorder, any information obtained from a screening assay would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPO at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. 101.

The question at issue is whether or not the broad general assertion that the claimed polypeptides might be used for *any* diagnostic application, *any* drug discovery or *any* toxicology test (in the absence of a disclosure of *which* diagnostic application, *which* drug discovery or *which* toxicology test) would be considered to be an assertion of a specific, substantial, and credible utility. For reasons set forth above the disclosure satisfies none of the three criteria *See In re Kirk*, 153 USPO 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the intention of the

statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.').

2. Answers to arguments in paper No: 27.5, on 12/18/02, No:30, on 01/28/03, and No:33 on 03/19/03.

Applicant submits the Clustal W alignment of kallikrein 11 (TLSP, hippostatin), a trypsin-like serine protease, and a keratinocyte trypsin-like serine protease with the claimed SEQ ID NO:1. (It is noted that identification of the sequences 1-7 cited in the Clustal W alignment could be found in the first page of Exhibit A).

Applicant argues in paper Nos: 27.5 and 30 that there is a substantial homology between the claimed SEQ ID NO:1 and the kallikrein family, a family consisting of members known to have undisputed utility, homology can be used to show a substantial likelihood that the claimed polypeptide is similarly useful, and that Applicant needs not show any more to demonstrate utility. Applicant asserts that SEQ ID NO:1 has 90% sequence identity with kallikrein 11, and 100% identical from residues L61 to N253 of SEQ ID NO:1 (Exhibit A and B of previous response of paper No:17), wherein kallikrein 11 has been shown to have serine protease activity, is a useful marker for distinguishing prostate cancer and benign prostate hypertrophy, and is a potential new biomarker for

prostate and ovarian cancer as shown in LocusLink ID 11012. Applicant recites *In re Brana,* and *In re Langer*, stating that the Examiner has not come forward with evidence showing a person of skill in the art would doubt the asserted utility.

The recitation of *In re Brana,* and *In re Langer* is acknowledged.

Applicant's arguments set forth in paper Nos.27.5, and 30 have been considered but are not deemed to be persuasive for the following reasons:

Based on 90% sequence identity of SEQ ID NO:1 with kallikrein 11, or 100% similarity with a fragment of kallikrein 11, wherein it is not known whether said fragment has any biological activity, one could not predict that the claimed SEQ ID NO:1 has the same function as kallikrein 11, based on the teaching of Bowie et al, Lazar et al, Burgess et al, and Bork, *supra*.

In paper No: 33, Applicant describes the contents of Exhibits A-K submitted with paper No:17, at the suggestion of the Examiner, since there was inadequate explanation of some of the Exhibits.

Applicant asserts that in Exhibit C, in the first alignment, amino acids R21 to I243 of the claimed SEQ ID NO:1 are aligned with a trypsin-like serine protease domain comprising 230 amino acids of gnl/CDD/7285), and in the second alignment, amino acids R22 to I243of SEQ ID NO:1 are aligned with a trypsin domain comprising 217 amino acids of gnl/CDD/7446. Applicant concludes that one would interpret the identification of both trypsin-like serine protease and trypsin domain within SEQ ID NO:1 as evidence that it is more likely than not, SEQ ID NO:1 would also have protease

activity because SEQ ID NO:1 has the functional domain necessary for protease activity.

Applicant asserts that in Exhibit F, Yousef et al, 2000, that TLSP (kallikrein 11), when aligned with other kallikreins, to contain the catalytic triad of serine proteases, His 62, Asp112 and Ser203, and that the same catalytic triad is also found in SEQ ID NO:1 at His65, Asp112, and Ser206. Applicant concludes that one would find the presence of the catalytic triad evidences that more likely than not that SEQ ID NO:1 also has serine protease activity.

Applicant asserts that in Exhibit G, Mitsui et al teach that residues I54-N282 of TLSP (kallikrein 11) in an expression system, which correspond to I25-N253 of SEQ ID NO:1, has enzymatic activity. Applicant asserts that in view of the high level of sequence homology between SEQ ID NO:1 and kallikrein 11, one would conclude that more likely than not that SEQ ID NO:1 also has serine protease activity.

Applicant asserts that in Exhibit H, Nakamura et al teach that the brain-type isoform 1 of kallikrein 11 may be used as a marker to distinguish prostate cancer and benign prostate hypertrophy (BPH), because all prostate cancer cell lines tested express only isoform 1, while both normal prostate and BPH tissues express both isoforms 1 and 2 of kallikrein 11. Applicant asserts that thus SEQ ID NO:1 would similarly be useful as a diagnostic marker for prostate cancer.

Applicant asserts that in Exhibit J, Gan teaches that the serine proteases have hydrophobic signal peptides of 16 to 33 residues, suggesting that they are secreted serine proteases., and that TLSP (kallikrein 11) has a kallikrein loop, residues P106 to

D109, PNKD, which is believed to interact with the substrate and thus determine the kallikrein enzymatic specificity. Applicant asserts that in view of the presence of the identical kallikrein loop in SEQ ID NO:1, one would conclude that more likely than not that SEQ ID NO:1 also has the same substrate specificity as TLSP.

Applicant asserts that in Exhibit K, Yousef et al, 2001, teach that the conserved regions around the catalytic triad are WVLTAAHC (emphasis added), DLMLL, and GDSGGPL (p.187-188). Applicant asserts that the comparable regions around the catalytic triad are WLLTAAHC (emphasis added), DLMLL, and GDSGGPL for TLSP (kallikrein 11) and WFLTAAHC (emphasis added), DLMLL, and GDSGGPL for SEQ ID NO:1. Applicant asserts that neither SEQ ID NO:1 nor TLSP (kallikrein 11) has the V residue, and that the F residue in SEQ ID NO:1 is a recognized conservative amino acid substitution for L residue present in TLSP (kallikrein 11). Applicant asserts that in all other instances, SEQ ID NO:1 and TLSP (kallikrein 11) follow the conserved sequence pattern for the kallikrein gene family. Applicant asserts that it is more likely than not that SEQ ID NO:1 is another member of the kallikrein gene family and another splice variant of kallikrein 11. Applicant concludes that thus SEQ ID NO:1 would be a serine protease, associated with cancerous prostate tissues, and useful for the diagnosis of prostate cancer.

It is noted that the LocusLink ID 11012 cannot be considered and is not entered, because MPEP 608.01(p) states that USPTO policy does not permit the USPTO to link to any commercial sites, since the USPTO exercises no control over the organization, views or accuracy of the information contained on these outside sites.

The recitation of Yousef et al, Mitsui et al, Nakamura et al, and Gan et al is acknowledged.

Applicant's arguments set forth in paper No: 33 have been considered but are not deemed to be persuasive for the following reasons:

Concerning Exhibit C, alignment of SEQ ID NO:1 with a trypsin-like serine protease domain comprising 230 amino acids of a trypsin-like serine protease (gnl/CDD/7285), and with a trypsin domain comprising 217 amino acids of trypsin (gnl/CDD/7446), there is no references or data supporting that these regions are trypsin-like serine protease domain or trypsin domain of the trypsin-like serine protease or trypsin, respectively, which confer the protease activity. In addition, even if these regions are trypsin-like serine protease domain or trypsin domain of the trypsin-like serine protease or trypsin, respectively, which confer the protease activity, it is noted that there are several differences in several amino acids at various positions between SEQ ID NO:1 and the trypsin-like serine protease domain or trypsin domain, and the effect of these differences on the protease activity is unpredictable, based on the teaching of Bowie et al, Lazar et al, Burgess et al, and Bork, *supra*.

Concerning Exhibit F, although the presumed catalytic triad is found in SEQ ID NO:1 at His65, Asp112, and Ser206, and although the catalytic triad His 62, Asp112 and Ser203 of kallikrein is necessary for serine protease activity, Applicant has not shown that said three amino acids are sufficient for conferring the serine protease activity to SEQ ID NO:1 (see further discussion on the conserved regions around the triad in the discussion of Exhibit K below).

Concerning Exhibit G, although residues I54-N282 of TLSP (kallikrein 11) in an expression system, which correspond to I25-N253 of SEQ ID NO:1, has enzymatic activity, it is noted that there are several differences of several amino acids in different positions between residues I54-N282 of TLSP (kallikrein 11) and I25-N253 of SEQ ID NO:1 (see first alignment in Exhibit A, wherein Query is SEQ ID NO:1, starting at amino acid residue 5, and Sbjct is hippostatin (kallikrein 11 or TLSP), starting at amino acid residue 38), and the effect of these differences on the serine protease activity is unpredictable, based on the teaching of Bowie et al, Lazar et al, Burgess et al, and Bork, *supra*.

Concerning Exhibit H, although the brain-type isoform 1 of kallikrein 11 may be used as a marker to distinguish prostate cancer and benign prostate hypertrophy (BPH), one cannot predict that SEQ ID NO:1 would similarly be useful as a diagnostic marker for prostate cancer, because Applicant has not shown that SEQ ID NO:1 is a kallikrein 11 isoform, and because different genes and different isoforms of a protein have different, independent expression.

Concerning Exhibit J, although the serine proteases have hydrophobic signal peptides of 16 to 33 residues, suggesting that they are secreted serine proteases, Applicant has not shown that SEQ ID NO:1 has a signal peptide. Further, it is noted that Gan et al teach that the kallikreins contain an insertion of 11 residues, the kallikrein loop, just before the active site residue asparate D (p.125, second paragraph). In other words, for the kallikreins, the kallikrein loops consists of 11 amino acid residues and not four amino acids as claimed. In addition, it is not clear how and based on what data,

and based on which asparate D as the active site residue, Applicant came to the conclusion that the PNKD sequence is the kallikrein loop. Moreover, even if the PNKD sequence is the kallikrein loop, although TLSP (kallikrein 11) has a kallikrein loop, residues P106 to D109, PNKD, which is believed to interact with the substrate and thus determine the kallikrein enzymatic specificity, and although SEQ ID NO:1 has the amino acid sequence PNKD, Applicant has not shown that said PNKD sequence ~~by itself~~ is sufficient to confer serine protease activity.

Concerning the conserved regions around the catalytic triad as taught by Yousef, 2001, in Exhibit K, it is noted that SEQ ID NO:1 is different from all of the members of the kallikrein family and trypsin-like serine proteases. In other words, there is no consensus sequence found in SEQ ID NO:1. Different from SEQ ID NO:1, which has the region WFLTAAHC, all sequences from different kallikrein family members, and trypsin-like serine proteases, e.g. sequence 1 to 7, all have the conserved region WLLTAAHC in the catalytic triad, as shown in the Clustal W alignment, or the conserved region WVLTAAHC in the catalytic triad of the kallikreins, taught by Yousef et al, 2001. Further, changing from Valine (V) of the conserved region WVLTAAHC of the catalytic triad of the kallikreins, taught by Yousef et al, 2001, to Leucine (L) of the corresponding region WLLTAAHC of kallikrein 11 is a conservative evolutionary change, as taught by Yousef et al, 2000, Genomics, 63: 88-96, Exhibit F, especially page 92, second column, bridging page 93. However, it is noted that different from Leu and Val both of which belong to the same family class of hydrophobic amino acids, Phenylanine (F) belongs to a different family class, i.e. the class of hydrophobic

aromatic amino acids, and thus the effect of replacement of Leucine(L) with Phenylalanine (F) is unpredictable.

There is no reference cited by Applicant supporting Applicant's assertion that the Phenylalanine (F) residue in SEQ ID NO:1 is a recognized conservative amino acid substitution for the Leucine (L) residue present in TLSP (kallikrein 11), wherein said substitution would not affect the property, conformation and biological activity of SEQ ID NO:1. Contrary to Applicant assertion, one cannot predict that a difference from L versus F in the critical catalytic triad region, in addition to numerous other differences in the amino acid sequence N-terminal of said WFLTAAHC region of SEQ ID NO:1, as shown in the CLUSTAL W sequence alignment, would not affect the conformation necessary for serine protease activity. It is well known in the art that different from L and V, which belong to the same family class of hydrophobic amino acids, F belongs to a different family class, i.e. the class of hydrophobic aromatic amino acids, and thus the effect of replacement of L with F is unpredictable. As discussed above and in previous Office action, the Lazar et al and Burgess et al references clearly demonstrate that even a single amino acid alteration can alter the function of a protein. Similarly, Ohannesian, D W et al, 1996, Biochem, 35, 14405-14412, teach that substitution of the critical L316 of the aminoacyl-tRNA synthetase with F316 has a deleterious effect on the catalytic efficiency of aminoacylation, whereas the deleterious effect was partially alleviated by a more conservative substitution of L316 with V316 (abstract and page 14408, second column, first paragraph). Assemat, K et al, 1995 (Protein Science, 4 : 2510-2516, especially p.2510, first column, first paragraph, page 2513, second column, two

paragraphs before last paragraph) teach that conservative substitution in the hydrophobic core can effect different biological function in different ways, and that intimate packing of hydrophobic side chain at internal positions is important for protein folding and stability, wherein subtle disruptions of the packed protein core can result in dramatic effects on both stability and function. Assemat et al further teach that substitution of F25 with L25 of thioredoxin results in a mutant unable to form an active phage complex.

In view of the above, it is more likely than not that the claimed SEQ ID NO:1 would not be a serine protease. Further, in the absence of any disclosed relationship between the claimed polypeptide of SEQ ID NO:1 and any disease or disorder and the lack of any correlation between the claimed polypeptide with any known disease or disorder, SEQ ID NO:1 could not be used for diagnosis of prostate cancer.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Rejection under 35 USC 112, first paragraph of claims 1, 18-20, 26 pertaining to lack of enablement due to lack of a well established utility remains for reasons already of record in paper No.21.

Applicant asserts that to the extent that the rejection under 112, first paragraph is based on the improper allegation of lack of patentable utility under 101, it fails for the same reason.

Rejection remains for the same reasons set forth under 101 rejection.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Rejection under 35 USC 112, first paragraph of claims 1(b), 20, 26, pertaining to lack of enablement for naturally-occurring allelic variants of SEQ ID NO:1, remains for reasons already of record in paper No.21.

Applicant argues that the claims recite not only that the polypeptides have at least 90% sequence identity with SEQ ID NO:1, but also have a naturally-occurring amino acid sequence, and that through the process of nature selection, nature will have determine the appropriate amino acid sequence.

Applicant argues that given the information provided by SEQ ID NO:1, one of skill in the art would be able to routinely obtain a naturally-occurring amino acid sequences having at least 90% sequence identity to SEQ ID NO:1 by screening a cDNA library or use appropriate PCR conditions for the relevant polynucleotides/polypeptides that already exist in nature. One of skill in the art need not make and test vast number of polypeptides that are based on the amino acid sequences of SEQ ID NO:1.

Applicant's arguments set forth in paper No. 19 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that the claimed SEQ ID NO:1 has not been shown to have serine protease activity, *supra.*

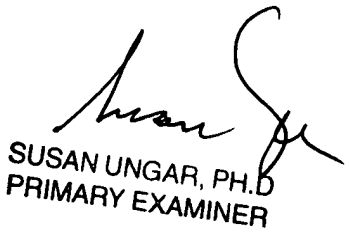
It is further noted that the specification has not disclosed how and what amino acids have been determined by nature to be substituted, deleted or added. The nature selection process however is not predictable.

The claims 1, 20, 26 read on naturally-occurring allelic variants of SEQ ID No:1, wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the nucleic acid or peptide, as well as insertions and deletions, provided that the resulted variation is up to 10% difference with SEQ ID NO:1. The specification does not disclose which amino acid are subjected to conservative or non-conservative substitution, or deletion, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. Thus the scope of the claims includes numerous structural variants that would exist in nature. No common structural attributes that identify the claimed variants are disclosed. No common functional attributes that identify the claimed variants are disclosed, because the function of SEQ ID NO:1 has not been convincingly demonstrated to be a serine protease, and because even a single amino acid substitution could dramatically affect the biological activity and characteristics of a protein, as taught by Burgess et al, Lazar et al, Tao et al, and Gillies et al, all of record.Thus one of skill in the art would have expected a vast number of unrelated sequences, with unknown function, would be obtained by hybridization or PCR techniques based on the polynucleotide sequence presumably encoding the claimed amino acid sequence of SEQ ID NO:1.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.



MINH TAM DAVIS

March 27, 2003